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Exploration for an Algorithm for Deintensification to Exclude the Retropharyngeal Site From Advanced Oropharyngeal Squamous Cell Carcinoma Treatment

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from ***JAMA Otolaryngology Head & Neck Surgery, April 1, 2016***

The objective of the study was to evaluate the prevalence of pathologic retropharyngeal adenopathy (RPA) in oropharyngeal squamous cell carcinoma (OPSCC) with relation to variables such as subsite, number of metastatic neck nodes, T and N classification, and the overall significant with regards to a deintensification protocol. Imaging (CT or PET-CT) was done on all patients four weeks before treatment with specified criteria establishing the presence of suspicious retropharyngeal nodes (≥1 cm or < 1 cm with avidity for FDG on PET-CT, presence of necrosis or evidence of extracapsular extension). Univariate and multivariate statistical analysis to determine associations of the variables with RPA metastases.

The population was 205 naïve patients with advanced (stage III-IV) OPSCC who underwent chemoradiotherapy (weekly carboplatin and paclitaxel and bilateral IMRT (70Gy)). The majority (96%) had base of tongue or tonsil tumors and 51% had T3-4 tumors. The majority of the population (86%) were classified as N2-3 and 83% were HPV +, with 35% as current smokers. Of the entire cohort, 37 patients (18%) had PRA. They were more frequent in tonsils tumors in comparison with base of tongue tumors (22% vs 14%, p>0.14). After controlling for all variables, RPA was more frequent, but did not achieve statistical significant, in T3-T4 tumors (40% vs 31%, p>0.15), N2-3 (35% vs 13%, p>0.11), or those near or involving posterior tonsillar pillar (42% vs 11%, p=0.5). Those patients with more than three lymph nodes achieved a statisticially significant increase in the risk of RPA (32% vs 6%, p<0.001)
Based on these results, the authors concludes that there is no association between T and N stage, tumor subsite and relation with posterior tonsillar pillar with presence of PRA, and that the only factor associated was the number of metastatic lymph nodes.

Critical analysis
The population is representative of OPSCC who are typical candidates for chemoradiotherapy (advanced local tumors located at base of tongue and tonsil with nodal involvement). However, most tumors were classified as stage IV (89%) and most of them where classified stage IV due to advanced nodal involvement (86% classified N2-3). This is also compatible with the higher number of HPV+ patients. Therefore, extrapolation of results to lower stage patients, those with a higher T classification or those with HPV- disease should be done carefully.

The determination of RPA was made by imaging techniques that are widely available, and interpretation of those images were made by a an expert radiologist with specific criteria. However, this is an imperfect method without histopathologic confirmation, which could influence the prevalence. Other studies have defined different limits to consider a lymph node suspicious. The authors do demonstrate that all the patients that met the CT criteria did show avidity for FDG in PET-CT, which may increase the trust in the CT results.

The results show that prevalence of PRA involvement is clinically different (although not statistically) between subsite, early and advanced T and N stage and posterior tonsillar pillar involvement to consider them factors associated with the presence of PRA. The difference was of 8% for subsite, 9% for T stage, 22% for N stage and 31% for pillar involvement. The absence of statistical significance is due to the low power of the study to detect these differences. As has been widely explored in clinical epidemiology, evidence of absence is not the same than absence of evidence.

Finally, other variables different to those explored in this study could affect the involvement of the retropharyngeal nodes. A rate of only 18% positivity of the retropharyngeal nodes involvement justifies the exploration of deintensification protocols in order to avoid long-term treatment sequelae.

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HPV status is associated with altered PIWI-interacting RNA expression pattern in head and neck cancer

Natalie Firmino, Victor D. Martinez, David A. Rowbotham, Katey S.S. Enfield, Kevin L. Bennewith, Wan L. Lam

from ***Oral Oncology, April 2016***

There are very few predictive or prognostic biomarkers for HNSCC. HPV-status is currently one of the few prognostic biomarkers available, despite a continual search for new molecular targets that may also serve as biomarkers.

Firmino et al. introduces a new class of non-coding RNAs called PIWI-interacting RNAs (piRNAs). PIWI refers to a class of proteins that are responsible for maintaining incomplete differentiation in stem cells. The name PIWI is derived from the wimpy gene in drosophila. These piRNAs have been shown to have a number of important functions including RNA silencing and post-translational epigenetic effects. This group sought to determine if there were any piRNAs that could serve as a predictive biomarker in HNSCC.

They analyzed 455 HNSCC samples and compared them to 43 non-malignant tissues samples. They found that 305 piRNAs were expressed in normal and malignant tissue. There were also 25 sequences

only in normal tissue and 87 only in tumors. Within the tumor samples they found that there were differences between HPV-positive and HPV-negative tumors in 11 piRNAs. When they looked at the HPV-positive tumors, they found a group of 5 piRNAs that were correlated with a significantly worse outcome. This 5 piRNA signature is proposed to be a potential prognostic biomarker for worse overall survival.

Strengths: This introduces a new kind of biomarker, the piRNA that may play an important mechanistic role in HNSCC.

Limitation: The proposed 5-piRNA signature needs to be tested against future tumors to validate their model.

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The Impact of Metastatic Lymph Nodes on Risk Stratification in Differentiated Thyroid Cancer: Have We Reached a Higher Level of Understanding?

Urken ML, Haser GC, Likhterov I, Wenig BM.

from ***Thyroid, April 2016***

This paper is a "Review and Scholarly dialog" that addresses the issue of metastatic lymph nodes on risk stratification in differentiated thyroid cancer. Citing recent studies that note that "the mere presence of a positive node is no longer deemed to confer an intermediate level of risk" and that it is the number, size, the ability to detect the lymph node clinically and the presence of extranodal extension (ENE) that all contribute to the patient risk profile, the goal of the publication "is to highlight some of the limitations and inherent inconsistencies of the parameters used to generate a risk profile for metastatic lymph nodes". In addition, the authors felt the need to specifically clarify the significance of extranodal extension. Selected articles addressing these risk factors provided the evidence and basis of the discussion.
Clinically evident lymph nodes. The 2015 ATA guidelines estimate the risk of recurrence for patients with a clinically evident lymph node at approximately 20%, Randolph et al (cited in paper) a range of 10-42% for N1 disease. Because of multiple factors such as the operator variability in performing ultrasound, the challenges in detecting nodes on clinical exam related to body habitus, surgeon experience and location of the nodes, "this parameter is prone to significant inconsistency".

Number of lymph nodes. Five or fewer micrometastatic nodes will assign a patient to the low risk group while more than 5 nodes less than 3 cm to the intermediate risk category. There are however numerous factors that will affect the accuracy of pathology reporting including surgical completeness of the compartmental dissection, inexperience of pathology residents processing the specimen, errors in pathologic assessment of nodes such as the failure of a pathologist to identify micrometastatic focus of cancer due to errors in sectioning prior to staining. These inconsistencies may degrade the value of using this parameter in determining prognosis.

Extranodal extension (ENE). Randolph et al recently identified in a meta-analysis that ENE conferred a range of risk between 15-32%. An article cited by Wu et al in 2015 showed the overall impact of ENE was magnified in patients over the age of 45 with 100% DSS when ENE was absent compared to 63% with ENE; in the entire cohort (included all ages) the 10 year DSS was 99% without ENE and 73% with ENE. Additional studies cited noted an additive effect when BRAF positivity was added to the findings of ENE. In review of several articles that address the issue of ENE it is noteworthy that there is tremendous variation in criteria used that results in the reporting of ENE, such as cancer cells extending out of the

node capsule, intraoperative evidence of cancer invading out of the node into adjacent structures with or without the need for that structure to be excised. As recently reported, there is also variation in reporting once the slides have been read by an experienced histopathologist, with only "fair" level of agreement. Recommendations were made to standardize the reporting of ENE by the American College of Pathologists.

Recent studies have also focused on the size of the lymph nodes as related to ENE and have shown that as many as 47% of nodes with ENE were less than 10 mm in size. A focus of thyroid cancer need not fill the entire node before it breaks out into the surrounding soft tissues. These smaller nodes with ENE may be more aggressive than a larger node with ENE, that being that early extension out of the capsule in a small node is a marker of aggressive biological behavior. 17/19 of the articles reviewed by the authors that addressed the issue of ENE demonstrate a negative prognosis when ENE is identified, providing support for the fact that it should be incorporated into staging and the risk of recurrence profile. The most recent ATA guidelines (2015) do not incorporate ENE into the three tiered risk stratification system. Patients with fewer than three nodes manifesting ENE are placed in the low end risk spectrum (2%) while those with more than three nodes with ENE are assigned to a higher risk category (40%). These recommendations were felt to be based on the findings of one French study that the authors of the review felt could not be extrapolated to the US population and that there were other issues with the study including the lack of key details related to the pathologic analysis of what constituted ENE.

Conclusion. The authors conclude that an important initiative would be the development of a clear definition of the pathologic criteria of what constitutes ENE, as well as stratification of the nodes that are identified as clinically evident. "It is then and only then, that we can begin to understand the impact of these various features on the biology of an individual's cancer and it's contribution to disease prognosis."

Strengths

- Excellent review of key articles
- Opinion of highly respected experts in the field

Limitations

- Retrospective review

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Definitive Surgical Therapy after Open Neck Biopsy for HPV-Related Oropharyngeal Cancer

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from ***Otolaryngology Head & Neck Surgery, April 2016***

A retrospective cohort (1998-2012) was used to evaluate the impact of prior open neck biopsy on the prognosis of patients with HPV+ OPSCC who then go on to receive definitive surgery +/- adjuvant radiation. 45 patients who underwent open biopsy were compared to 90 matched controls.

Inclusion criteria included 1) excisional or incisional biopsy performed as a separate operative procedure <1yr prior to definitive treatment, 2) primary surgical treatment for both the neck and the primary tumor

(+/- adjuvant radiation), 3) minimum 2 yr followup. Matched controls who did not undergo open biopsy instead underwent FNA, core-needle biopsy or biopsy at the primary site to obtain pathologic diagnosis.

Neck dissections were performed concurrently with transoral primary tumor resection. SND of levels II-IV was performed with resection of additional neck structures as required. Previous open biopsy incision and underlying subcutaneous scar tissues were excised as well as a small cuff of SCM and/or other neck musculature as indicated. Should pathology necessitate adjuvant treatment, radiation was dosed at 60Gy to pathologically involved lymph node levels and 52-54Gy to uninvolved levels. For necks with reported tumor spillage, the entire neck received 60Gy. 88% of all patients received chemotherapy (of these: 84% cisplatin alone, in the control group other agents included cetuximab (3), carboplatin+paclitaxel (2), cetuximab+docetaxel (1), in the open biopsy group other agents included cisplatin + cetuximab (1).

Selected results:

- 91% of open biopsies were performed outside of the Washington University system and subsequently referred. Of the open biopsies, 62% presented with unknown primary. Of the control group, 44% presented with unknown primary. All primaries were subsequently found during operative endoscopy.
- 18% of patients who underwent open biopsy were incisional biopsies where lymph node was either partially removed or removed piecemeal. In at least 3 cases (7% of open biopsy group), there were tumor deposits in the excised dermal scar. One of these was an incisional biopsy, the other 2 were excisional biopsies.
- There were no significant differences in complications after neck dissection between the two groups except 3 patients in the open biopsy group required flap reconstruction to repair cervical skin defects.
- No significant differences were found in 5 yr Kaplan Meier survival estimates of DFS, OS, DSS between open biopsy and control groups (93% vs. 91%, 98% vs. 97%, 98% vs. 99% respectively).
    - in the open biopsy group there were no local or regional recurrences
        - 3 distant failures (7%). Two received adjuvant radiation. One died of pericardial metastasis prior to receiving adjuvant treament
        - 4 patients in this group did not received adjuvant radiation. One died prior to treatment as listed above. The other 3 were free of disease at least 27.2 mo later. All 3 had excisional biopsies with no ECS and no additional lymph nodes were identified at the time of neck dissection.
    - in the control group there were
        - no local failures
        - 2 regional failures (2%) - Neither received adjuvant radiation.
        - 5 distant failures (6%). All were stage IVA. All received adjuvant treatment (3 with CRT, 2 with radiation alone)

Authors final recommendations:
For patients with HPV-related OPSCC who present after open neck biopsy: 1) completion neck dissection 2) previous incision should be excised given the risk of dermal seeding 3) adjuvant treatment should be determined in a multidisciplinary fashion.

Strengths

- This paper certainly adds to our limited literature on how to manage patients who present with open biopsy (excisional or incisional) in HPV-associated OPSCC. With the rise in HPV-related disease this is a dilemma that is encountered more and more frequently.
- Includes a nice table with all previous studies evaluating previous open biopsy in patients who ultimately present with a diagnosis of HNSCC. Their conclusion from this literature review (with heterogeneity including multiple subsites, varied open biopsy methods, varied treatment paradigms, some with unknown HPV status) is that it appears that the addition of radiation, either definitive or in the adjuvant setting, is beneficial. Nonetheless, this paper demonstrates excellent outcomes with definitive surgical management and appropriate adjuvant therapy.

Weaknesses

- Small sample size and a difference in DFS of at least 20% between open biopsy and control would be necessary to detect statistical significance
- Cannot be extrapolated to HPV negative disease or non OPSCC subsites.

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Increase in Primary Surgical Treatment of T1 and T2 Oropharyngeal Squamous Cell Carcinoma and Rates of Adverse Pathologic Features: National Cancer Data Base

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from ***Cancer May 2016***

The incidence of squamous cell carcinoma (SCCA) of the oropharynx (OP) is rising in large part due to the HPV associated disease. Controversy exists as to the most appropriate treatment. Over the years primary surgery and primary radiation have been considered the standard with studies in 2000's demonstrating survival benefit of chemoradiotherapy thus swinging the pendulum. Recently there has been a renewed interest and enthusiasm for primary surgery as a treatment for T1 and T2 OP carcinoma. This has been driven in large part because those presenting with HPV related OP cancer tend to present with earlier stage primary disease (T1 and T2) and present at a younger age than those who are HPV negative thus creating a desire to minimize short and long term treatment effects while maintaining excellent prognosis. The main outcome of the current study was to access the choice of primary treatment modality (surgery vs radiation) in treatment of T1 or T2 SCCA of the oropharynx. A secondary outcome was the presence of adverse pathologic features among those patients who underwent primary surgical treatment including positive margins, extracapsular extension within a lymph node, T3-4 or N2-3 on final pathology. In this study, the National Cancer Data Base was reviewed to identify those patients with patients with T1 to T2 SCCA of the OP who were treated from 2004 through 2013. They were categorized as receiving primary surgical or primary radiation-based treatment. Trends in treatment selection and factors related to the selection of primary surgery were examined. The rates of adverse pathologic features including positive surgical margins, extracapsular spread (ECS), and advanced T and N classifications after surgery were analyzed. 8768 patients were identified between 2004 and 2013. 47% of patients presented with clinically classified T1 tumors and 53% presented with T2 tumors, whereas 26% of patients had clinically or radiographically classified N0 disease, 23% had N1 disease, 47% had

N2 disease, and 3% of patients had N3 disease at the time of presentation. 49% were treated at community cancer programs, 26% of patients were treated at higher volume hospitals (see >50 patients with SCCA of the OP), and 34% were treated at low-volume hospitals (≤10 patients). 68% of patients (5967 patients) underwent primary surgical treatment. From 2004 through 2013, the use of the primary surgical approach increased over time from 56% of patients in 2004 to 82% in 2013. Patients treated at academic hospitals were treated with a primary surgical approach more often than those treated at community hospitals (74% vs 62%; P<.0001), and patients treated at the highest volume hospitals were treated with a primary surgical approach more often than those treated at the lowest volume hospitals (78% vs 59%; P<.0001). In patients treated with surgery, positive surgical margins were present in 24% and ECS in 25% of patients. The rate of positive surgical margins decreased over time (P<.0001) and was observed less often at high-volume centers (P<.0001). This study points out that at the current time patients with ECS, positive margins, or advanced primary (T3 or T4) or nodal disease (N2 or 3) that radiation or chemoradiation is indicated post operatively. Thus in certain cases with high risk features primary surgery can actually lead to escalation of therapy (tri therapy) thus suboptimal treatment selection may ultimately be leading to escalation of adjuvant therapy. Important weaknesses of the study include: several cases were excluded due to insufficient data, as "tonsillectomy" was considered in the surgical group this may have led to the higher rate of positive margins as it was difficult to always know if this was done with oncologic intent of complete resection or that of diagnosis/biopsy, lastly, the HPV status was not available for review in this group of patients and would have been very interesting when analyzing treatment trends. In summary, primary surgical treatment of T1 and T2 SCCA of the OP is increasing, positive margins are more common in low volume centers, and care should be taken in pre operative evaluation to access for those cases with high risk features that will result in the need for post operative chemoradiation and actually lead to escalated therapy instead of the intended de-escalation goals.

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